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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,013	NGUYEN ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed January 14, 2003. Currently, claims 1-3 are pending.

2. An examination of this application reveals that applicant is unfamiliar with patent prosecution procedure. While an inventor may prosecute the application, lack of skill in this field usually acts as a liability in affording the maximum protection for the invention disclosed. Applicant is advised to secure the services of a registered patent attorney or agent to prosecute the application, since the value of a patent is largely dependent upon skilled preparation and prosecution. The Office cannot aid in selecting an attorney or agent.

Applicant is advised of the availability of the publication "Attorneys and Agents Registered to Practice Before the U.S. Patent and Trademark Office." This publication is for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

4. The disclosure is objected to because of the following informalities.

A) Page 1, line 15 recites "in cells ans tissues." It is presumed that the passage should read "in cells and tissues."

Appropriate correction is required.

New Matter

5. The amendment filed January 7, 2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows.

On January 7, 2002, Applicant's filed a sequence listing with 3 sequences to be entered into the case. Each of these sequences do not appear to be originally filed in the application and appear to constitute new matter. In a letter dated January 9, 2003, Applicants indicate that SEQ ID NO: 1-3 are probes 1-3. The response asserts that probes 1-2 are portions of exons 7-8 of the SMN gene. The examiner acknowledges that this assertion is correct, however, these sequences were not present in the originally filed application. The sequence of the exons 7-8 of the SMN gene were known at the time the invention was made, however, the exact sequence of probes 1-2 were not taught in the instant specification at the time the invention was made. The response attempts to point to support by identifying specific excerpts from the specification which discuss the SMN gene taught by Lefebvre. This disclosure does not

provide the sequence of the probes claimed in the instant application. The probes 1-2 are not the full length exons 7-8, but rather portions of exons 7-8. Therefore, the specific sequences were not disclosed at the time the invention was made. The response filed January 9, 2003, clearly states, "the sequence of probes 1 and 2 were specified but not listed in the application because they are portions of the whole sequences of exons 7 and 8 respectively, already listed in the reference publication by Lefebvre et al., Ref. #16 stated in the reference list of the application."

As provided in MPEP 608.01 (p), "An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, Ex parte Schwarze, 151 USPQ 426 (Bd. App. 1966)." Moreover, "Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973)." Therefore, the instant specification does not appear to include a proper incorporation by reference. Thus, the essential subject matter may not be added to the instant specification.

Similarly, SEQ ID NO: 3 (probe 3) is not disclosed in the instant specification. While the sequence may be present in the art, this is not disclosure in the instant application.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting SMA by detecting the absence of SMN exons 7 and 8 does not reasonably provide enablement for a method for controlling mRNA concentrations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a quantitative method for detecting SMA by detecting the absence of SMN exons 7 and 8 where the quantitative method may be used "in the control of mRNA concentrations in the future gene therapy of patients with SMA."

The art teaches the detection of deletions in exons 7 and 8 of the SMN gene for detection of SMA. Lefebvre et al. (Cell, Vol. 80, pages 155-165, January 13, 1995) teaches the identification and characterization of a spinal muscular atrophy-determining gene. On page 159, Lefebvre teaches SSCP analysis on SMA patients which illustrates that deletions are present only in SMA patients but are not present in control patients.

The specification fails to provide any guidance to gene therapy.

Neither the art nor the specification provides the skilled artisan how to make and use gene therapy for SMN gene which is applicable with SMA patients. The claim is specifically directed to "future gene therapy of patients with SMA." The state of the art, with respect to gene therapy is unpredictable. Undue and unpredictable experimentation would be required to perform gene therapy on SMA patients using the SMN gene. Thus, at the time the invention was made, the skilled artisan would be unable to practice the invention as a whole.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-2 are indefinite over the recitation "(quantifying by means of BioImager or ELISA with colorimetric detection)" because it is unclear whether the

claims are limited to these two particular quantification means or whether the claims a merely provide two suggestions for quantification methods.

B) Claims 1-2 are indefinite over the recitation "BioImager" because it is unclear whether the recitation is referring to a specific product or whether the claim is merely directed to any particular device which provides an image of biological material.

C) Claims 1-2 are indefinite over the recitation "the labeled nucleotide probes 1 and 2" because "the labeled probes lacks proper antecedent basis." The claim does not previously refer to any labeled probes. This rejection may be easily over come by amending the claim to recite "utilizing labeled nucleotide probes,,,:,

D) Claims 1-2 are indefinite over the recitation "probes 1 and 2." The specification does not describe probes 1 and 2 in any particular manner. The specification has not provided any sequence identifier to describe probes 1 and 2 nor has the specification described probes 1 and 2, therefore, it is unclear what constitutes probes 1 and 2. Moreover, the claim recites "probes 1 and 2 directed at exons 7 and 8 respectively." It is unclear whether the probes are exons 7 and 8 or whether the probes are smaller fragments of exons 7 and 8 which may be used to detect exons 7 and 8.

E) Claims 1-2 are indefinite because the method lacks positive process steps which are required and a complete method. The claims do not provide any method steps for quantitatively measuring specific mRNA. Moreover, there is no final step to the method which completes the method. For example, a method with positive process steps would include: A quantitative method for measuring mRNA of the SMN gene for the diagnosis of spinal muscular atrophy (SMA) comprising a) obtaining a sample from

a human containing mRNA from SMN b) hybridizing a probe of SEQ ID NO: 1 or 2 with the sample from a human c) quantitatively measuring the mRNA wherein the presence of **** mRNA is indicative of SMA.

F) Claims 1-2 are indefinite over the parenthetical (labeling with 32P-dCTP and biotin) because it is unclear whether this is a limitation of the claim or whether the claim is merely suggesting to possible labels. Furthermore, it is unclear whether the labeled probe would contain both a 32P-dCTP and a biotin label or whether only one label is required.

G) Claims 1-2 are indefinite over the recitation "for the molecular diagnosis of SMN" because it is unclear how the ordinary artisan would use the information for the molecular diagnosis of SMN.

H) Claim 2 is indefinite because it is unclear how the claim is intended to further limit or claim the invention. The claim requires that the method of Claim 1 may be used in the control of concentration in the future gene therapy of patients with SMA. It appears that the claim does not require the use of the method for control because the claim state "may." Furthermore, it appears that the claim does not believe that gene therapy is presently possible based upon the use of the word "future." Therefore, the claim appears to be claiming something which has not yet been enabled.

I) Claim 3 is indefinite because it is unclear what is being claimed. It is unclear whether a method of making kits or a quantitative method based on the measurement of specific mRNA or a method for controlling mRNA concentration or methods for methods of detecting deletions or mutation of the gene.

J) Claim 3 is unclear because "the gene(s)" lacks proper antecedent basis. It is unclear which genes are being referred to. The claim fails to describe a single gene. Based upon the disclosure of other claims, only a single gene has been described. Therefore, it is unclear what the "genes" is referring to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lefebvre et al. (Cell, Vol. 80, pages 155-165, January 13, 1995) or Van der Steege (Lancet, Vol. 345, pages 985-986, April 1995) in view of Feuerstein et al. (US Pat.

5,635,351, June 3, 1997) and in further view of Lefebvre et al. (Genbank Accession Number U438836, May 16, 1996).

Lefebvre et al. (herein referred to as Lefebvre) teaches the absence of the SMN gene in SMA patients. Lefebvre teaches using SSCP analysis of amplified exons 7 and 8 in 229 SMA patients. Lefebvre teaches 213 or 229 SMA patience lacked the SMN exons 7 and 8 on both chromosomes as compared to 0 of 246 controls. Figure 5 illustrates the SSCP analysis of amplified exons 7 and 8.

Van Der Steege et al. (herein referred to as Van Der Steege) teaches analyzing SMN gene for mutations using SSCP analysis and mismatch-PCR assay. Van Der Steege teaches a whole exon 7 and 8 deletions were present in SMA patients.

Lefebvre does not specifically teach using a probe directed to the deletion region for detection of the presence or absence of the nucleic acid.

However, Feuerstein teaches preferable methods of detection involves hybridization of a nucleic acid probe with a nucleic acid found in the deletions (col. 2, lines 65-68). Feuerstein teaches that the probes may be differentially labeled so that they may be distinguished (col. 3,lines 18-20). Probes bearing fluorescent labels are preferred with direct-labeled probes being most preferred (col. 3, lines 20-21). Feuerstein teaches assaying for the presence or absence of the probe, one can detect the presence or absence of the target. Feuerstein specifically teaches that well known methods for detecting the presence or absence of deletions include hybridization with probes that are specific to nucleic acid sequences within the deleted regions, and detection of single strand conformation polymorphisms (SSCP) (col. 6, lines 55-68).

Finally, detection and quantification of the hybridization complex formed between the probe and the sample nucleic acid indicates the presence or amount of the deletion nucleic acid sequence (col. 7, lines 55-60). Feuerstein teaches that the nucleic acid probes may be labeled using fluorescent dyes or enzymes (as commonly used in an ELISA) (col. 13, lines 40-45).

Moreover, Lefebvre teaches the survival motor neuron (SMN) gene exons 7 and 8. SEQ ID NO: 1 of the instant application is 100% identical to positions 211-262 of the sequence of Lefebvre. However, Lefebvre teaches that exon 7 is positions 209-262. Moreover, SEQ ID NO: 2 of the instant application is 100% identical with potions 707-761 of the sequence of Lefebvre. However, Lefebvre teaches exon 8 is positions 707-1266.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the method of detecting the presence or absence of exons 7 and 8 of the SMN gene using the method of Lefebvre or Van Der Steege by modifying the method to use probes as taught by Feuerstein in view of Lefebvre. The ordinary artisan would have recognized that, at the time the invention was made, exon deletions could be accurately and quantitatively detected using probes to the deleted exons. Feuerstein specifically teaches that at the time the invention was made, that the detection using probes to deleted regions and detection with SSCP were equivalent methods for detecting deletions. Thus, the skilled artisan would have been motivated to have detected the absence of exons 7 and 8 in individuals to determine the SMA status. Since the art teaches that deletions of exons 7 and 8 are found only in

SMA patients, detection of the deletions would provide an accurate means of detecting whether an individuals was at risk or had SMA.

Conclusion

10. No claims allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
July 13, 2003

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